Highlights from
IMS 20th meeting 2023

Carolina Terragna

Clonal Evolution

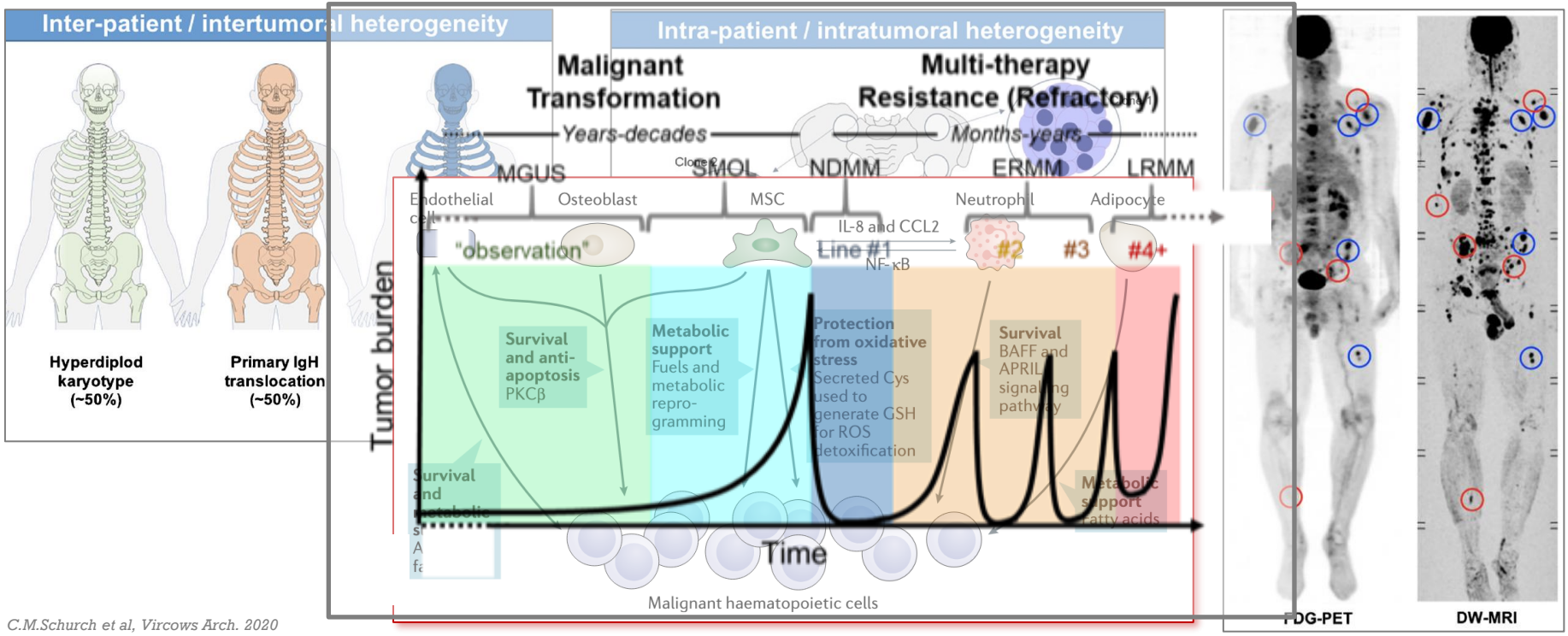
30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Carolina Terragna

nothing to disclose

outline of the presentation

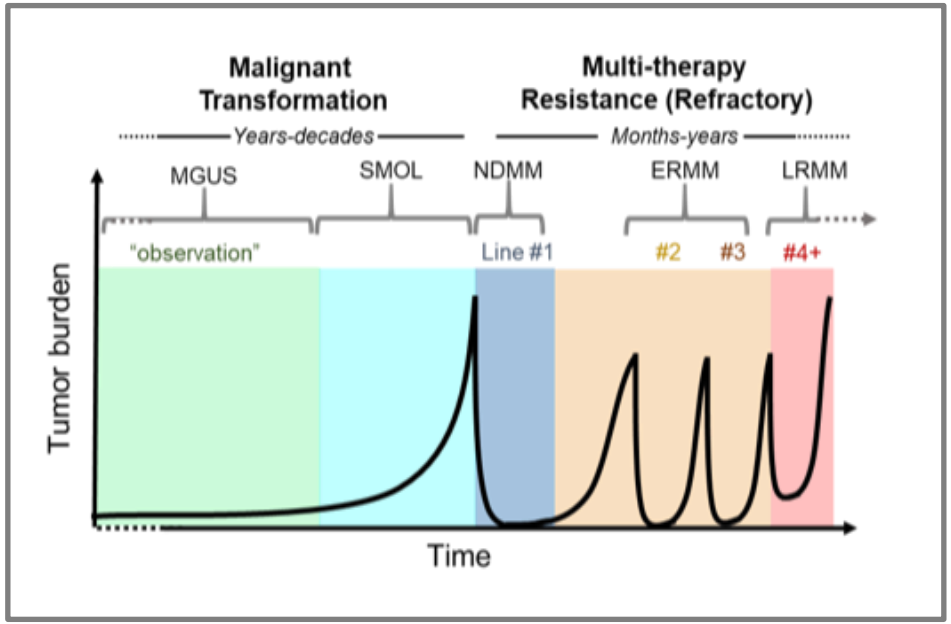
clonal evolution & heterogeneity of Multiple Myeloma



C.M.Schurch et al, Vircows Arch. 2020
S. Mendez Ferrer et al., Nature Rev.Cancer 2020

outline of the presentation

the disease dynamics of MM: clonal evolution



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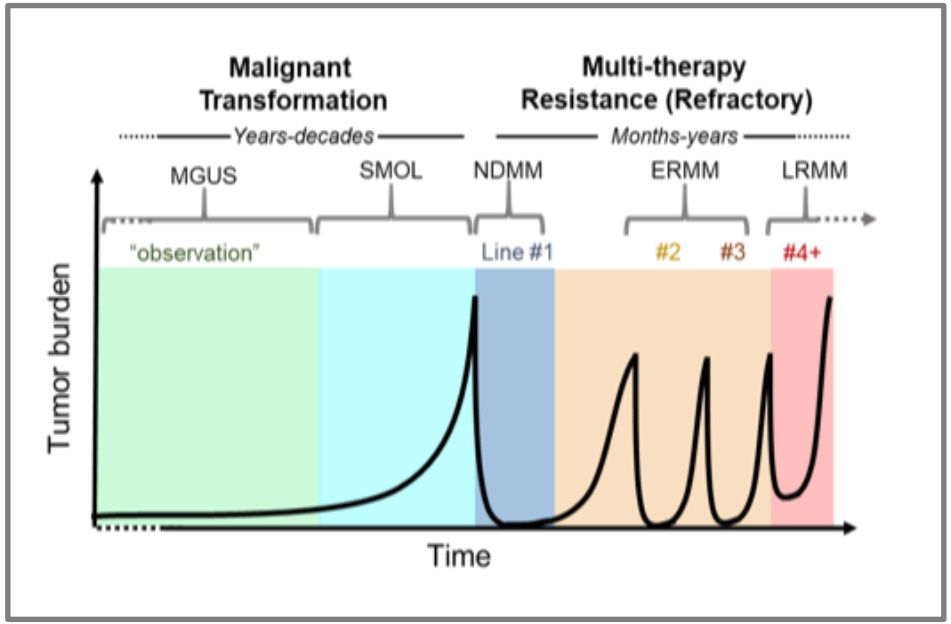
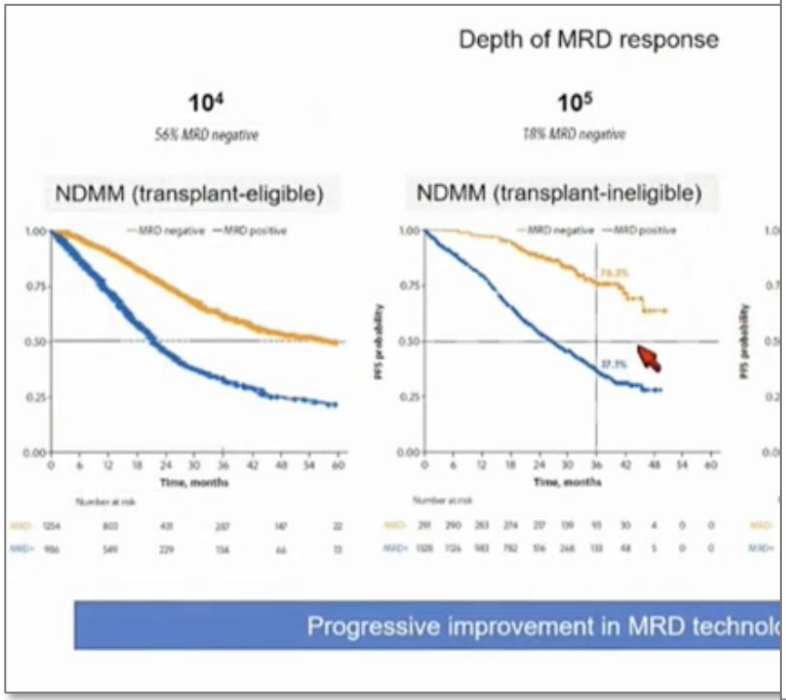
the disease dynamics of MM: clonal evolution

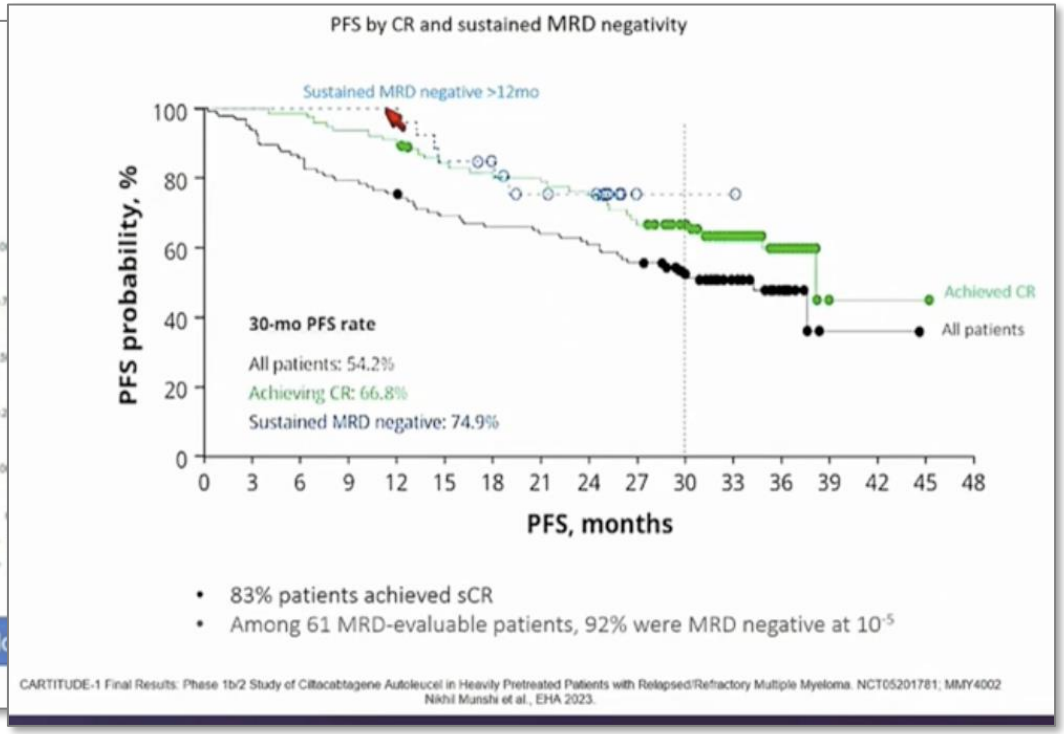


1. ***MRD*** is the result of the therapy-induced selective pressure
2. the ***origin*** of clonal heterogeneity
3. disease ***dissemination***: a role for CMMCs?

selective pressure & MRD

MRD & clinical outcome

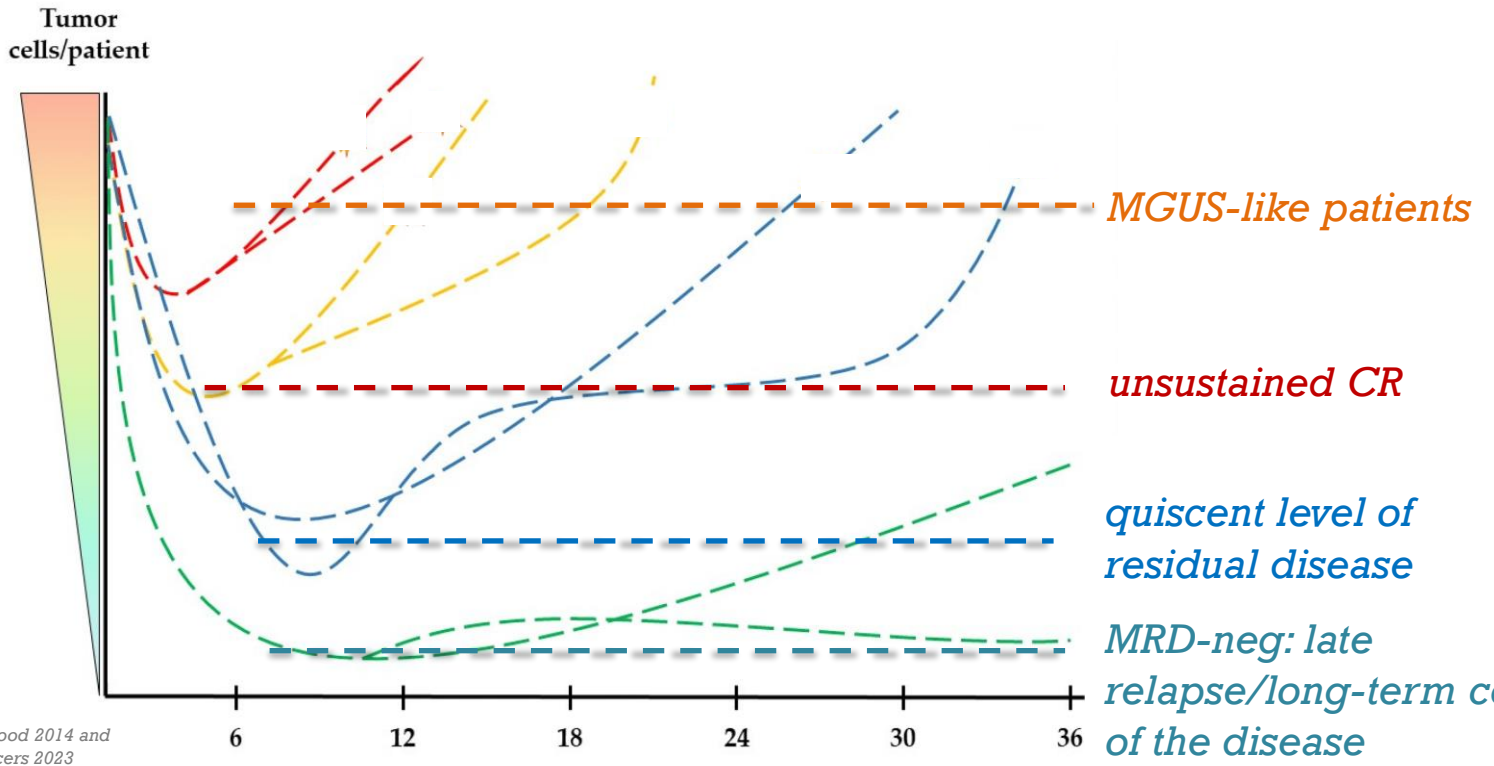




R.Tiedemann, IMS 2024

selective pressure & MRD

the Minimal Residual Disease

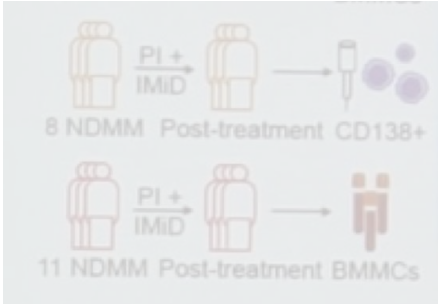


adapted from B.Paiva et al., Blood 2014 and
A. Medina-Herrera et al., Cancers 2023

selective pressure & MRD

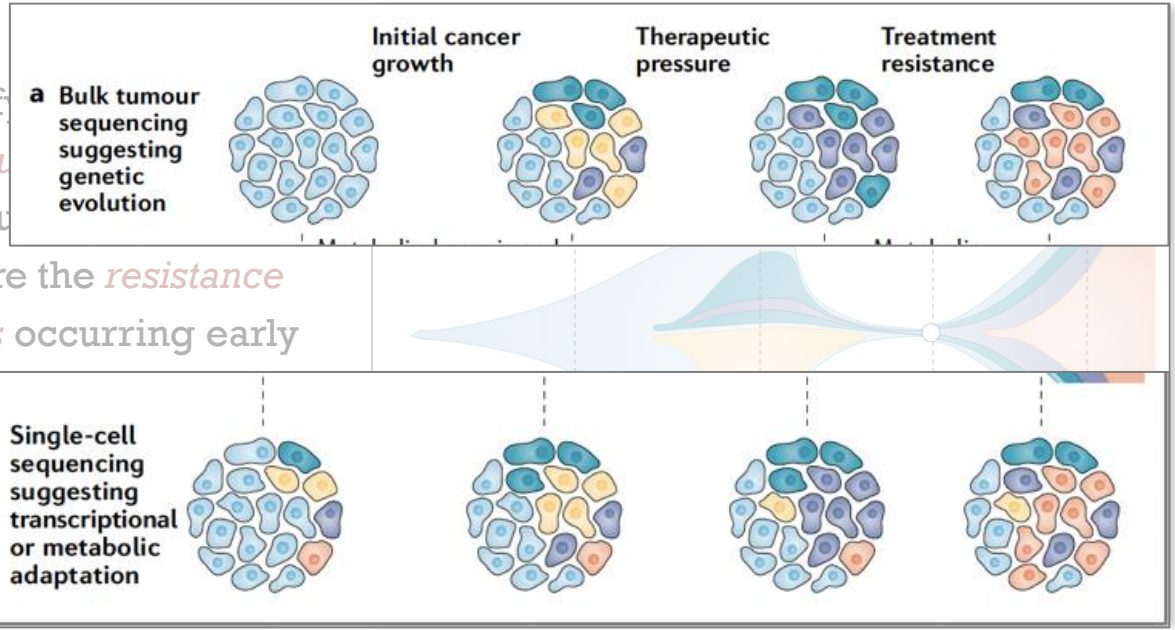
abstract session 4, GENOMICS:

J.Cui et al., «*Identification of therapy-induced clonal evolution and resistance pathways in MRD clones*»



scRNA-seq

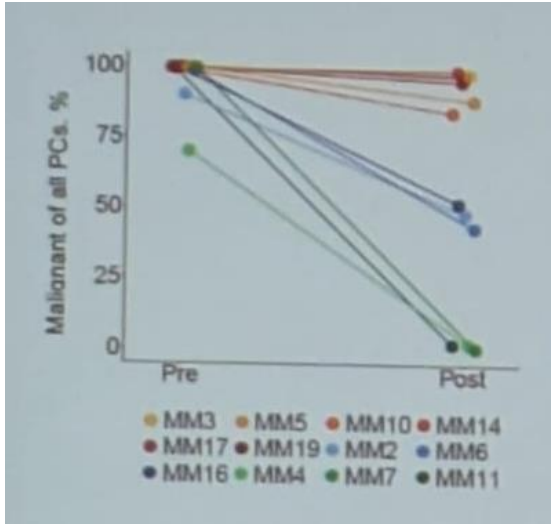
1. to identif
   architectu
   after indu
2. to explore the *resistance pathways* occurring early after u



J.Cui et al., IMS 2024
J.C. Marine et al, Nat.Rev.Cancer, 2020

selective pressure & MRD

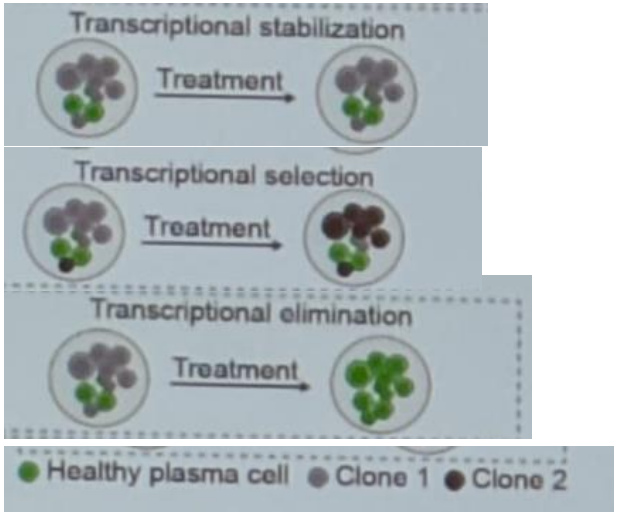
transcriptional evolution post-treatment



MRD-pos pts (42%), with a therapy-resistant PCs clone (>90% malignant PCs)

MRD-pos pts (33%), with clonal selection (>50% malignant PCs)

MRD-neg pts (25%), with therapy-sensitive PCs (>90% normal PCs)



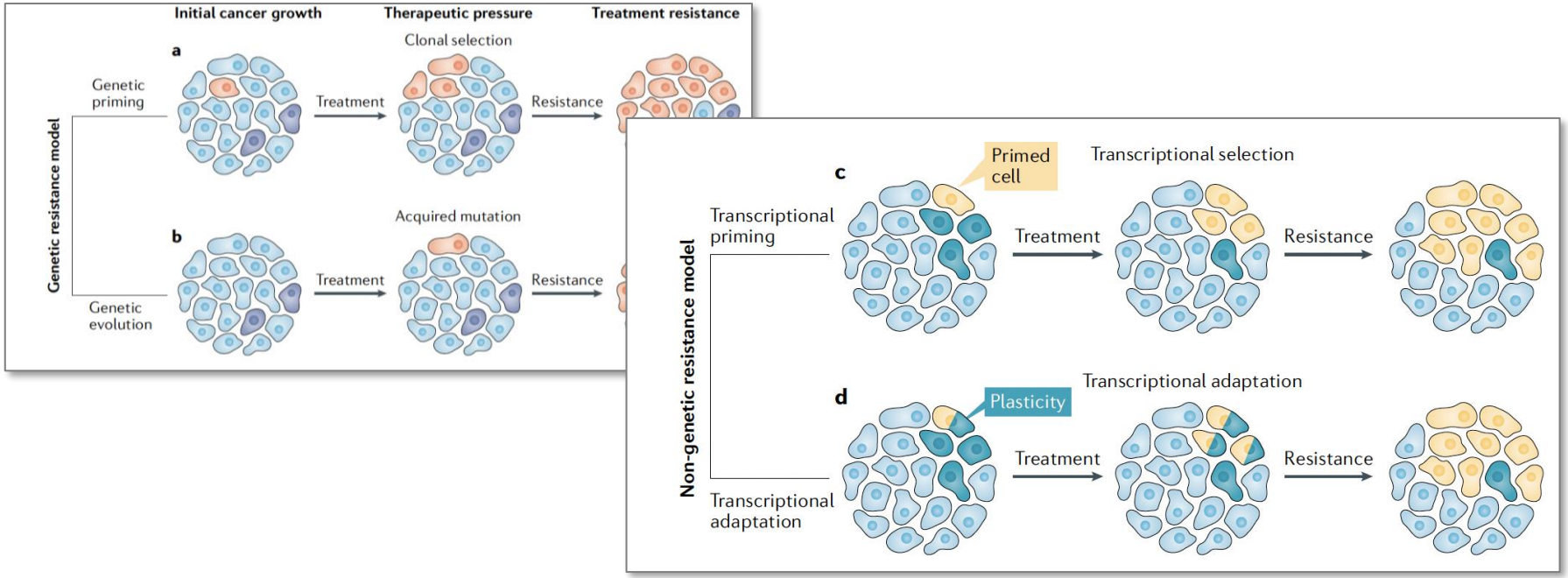
➔ distinct resistance-related deregulated pathways in MRD clones:

- ***resistant*** PCs => cell cycle-related, unfolded protein response and hypoxia
- ***selected*** PCs => NF-kB and anti-apoptotic

J.Cui et al., IMS 2024

selective pressure & MRD

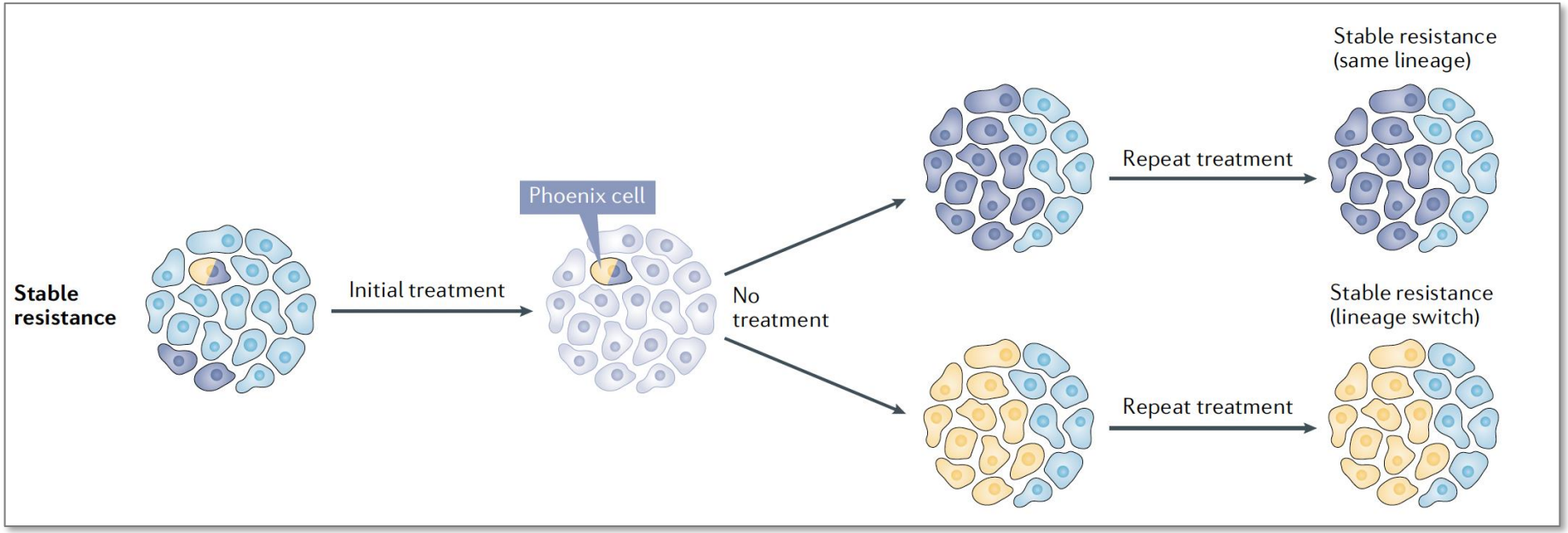
non-genetic mechanisms of evolution => transcriptional & metabolic ADAPTATION



J.C. Marine et al, Nat.Rev.Cancer, 2020

the origin of clonal heterogeneity

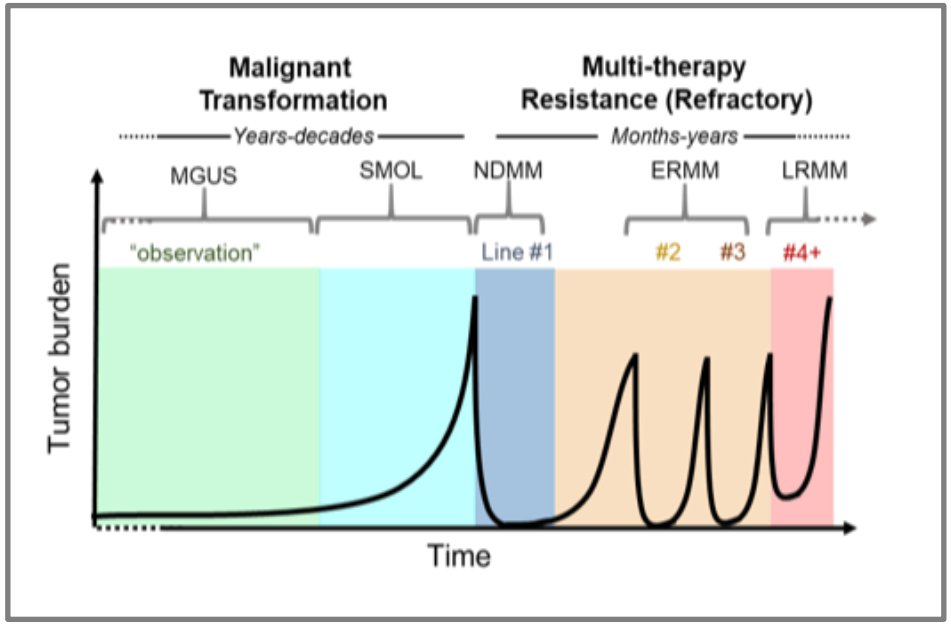
MRD & chemoresistance



J.C. Marine et al, Nat.Rev.Cancer, 2020

outline of the presentation

the disease dynamics of MM: clonal evolution



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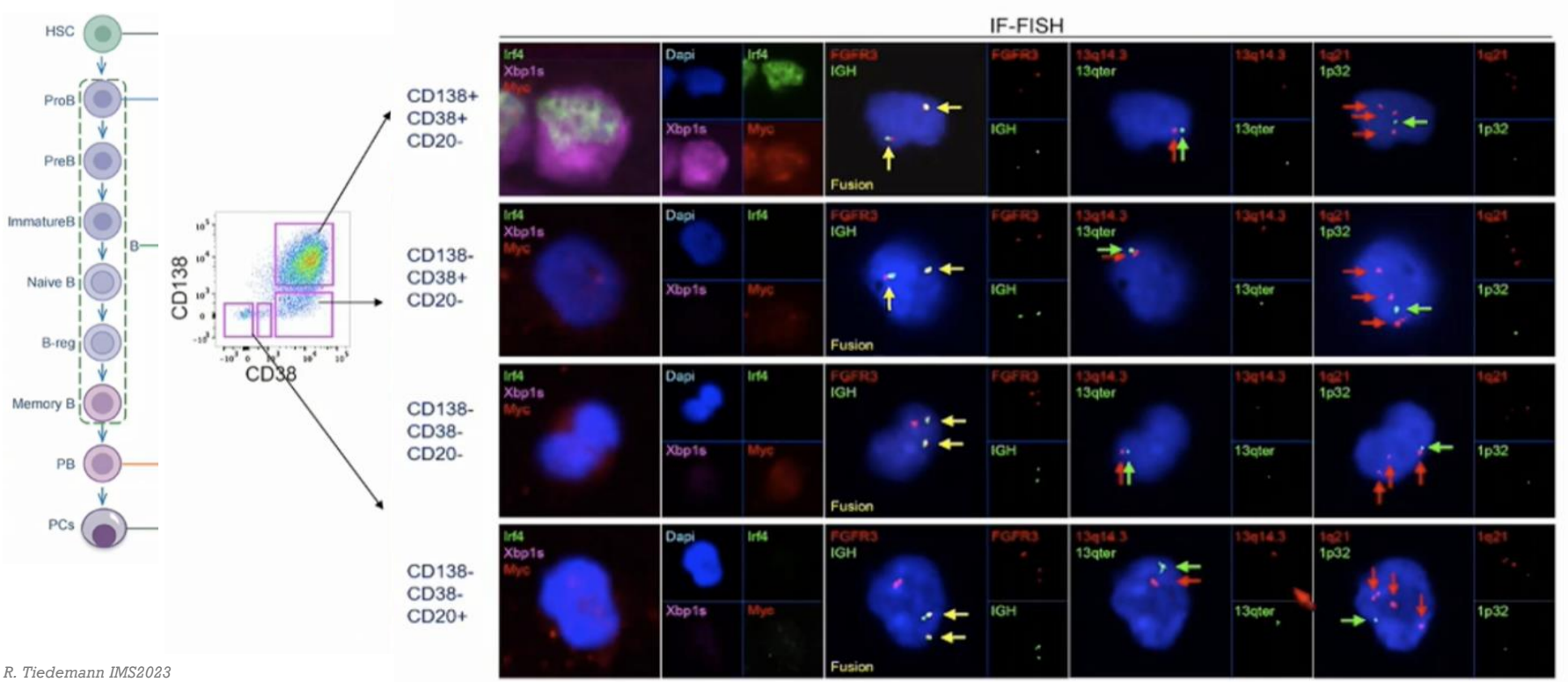
the origin of clonal heterogeneity

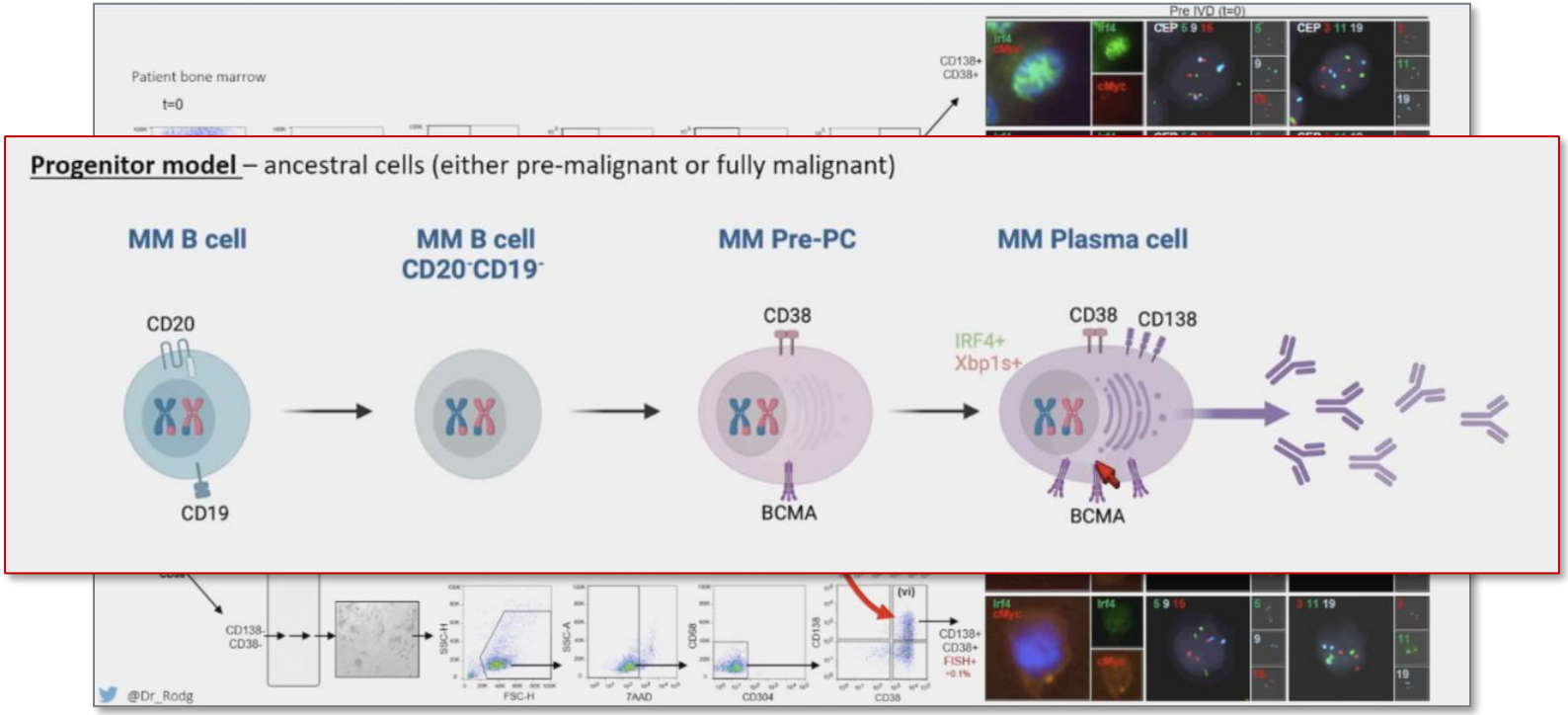
MM: more than just plasma cells



R. Tiedemann IMS2023

the origin of clonal heterogeneity

1. MM progenitors can differentiate into PCs



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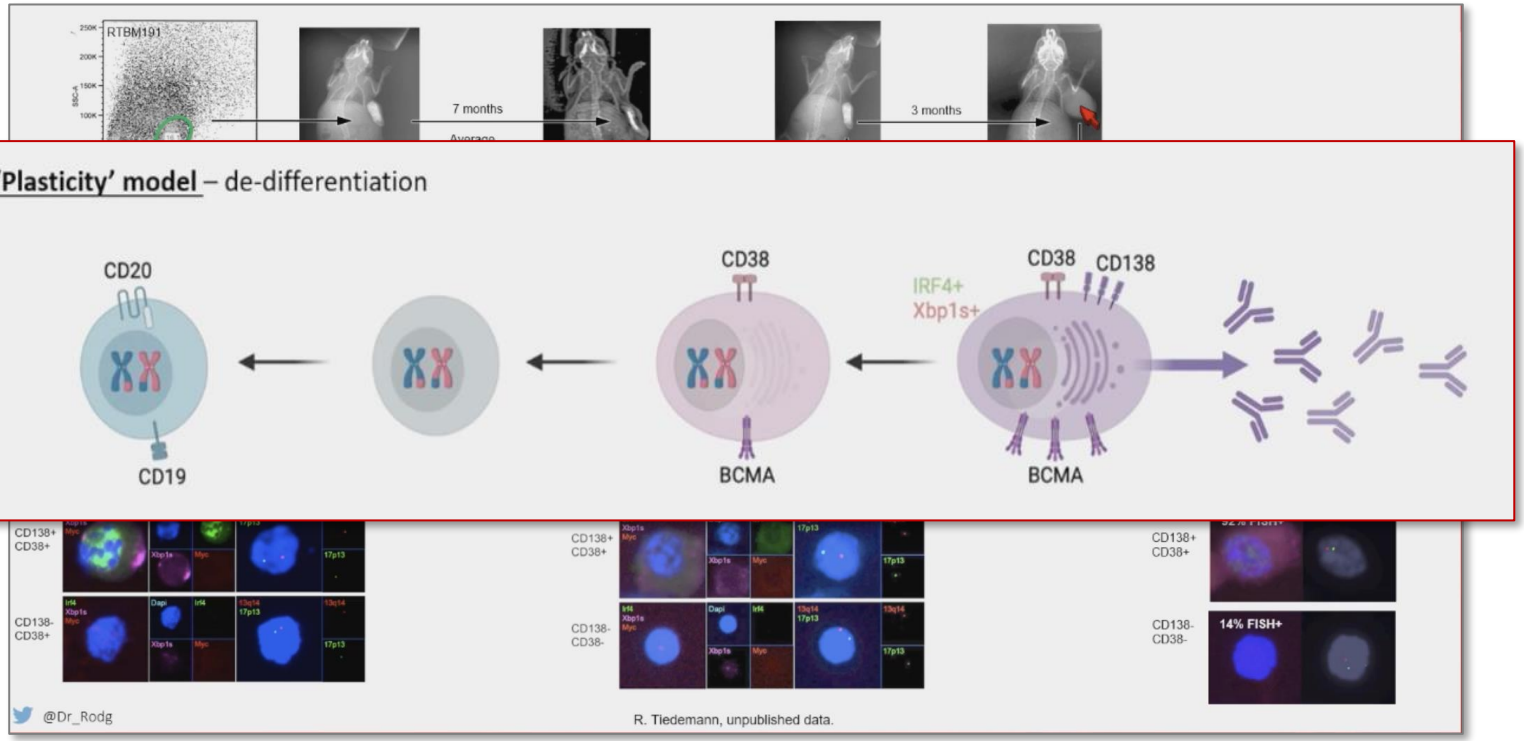
the origin of clonal heterogeneity

2. MM PCs can de-differentiate *in vivo*



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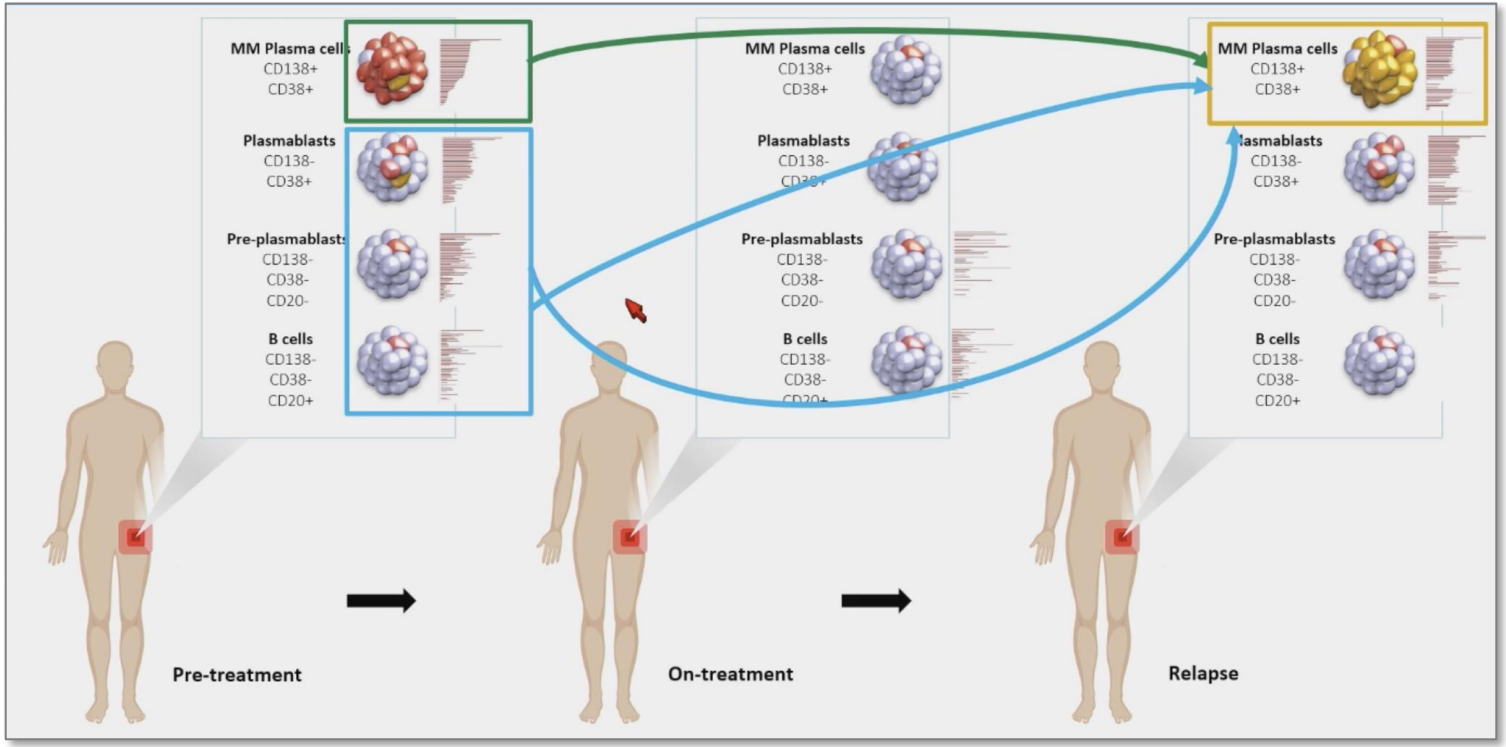
the origin of clonal heterogeneity

MM B-cells and pre-PCs contribution to clinical relapse



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the origin of clonal heterogeneity

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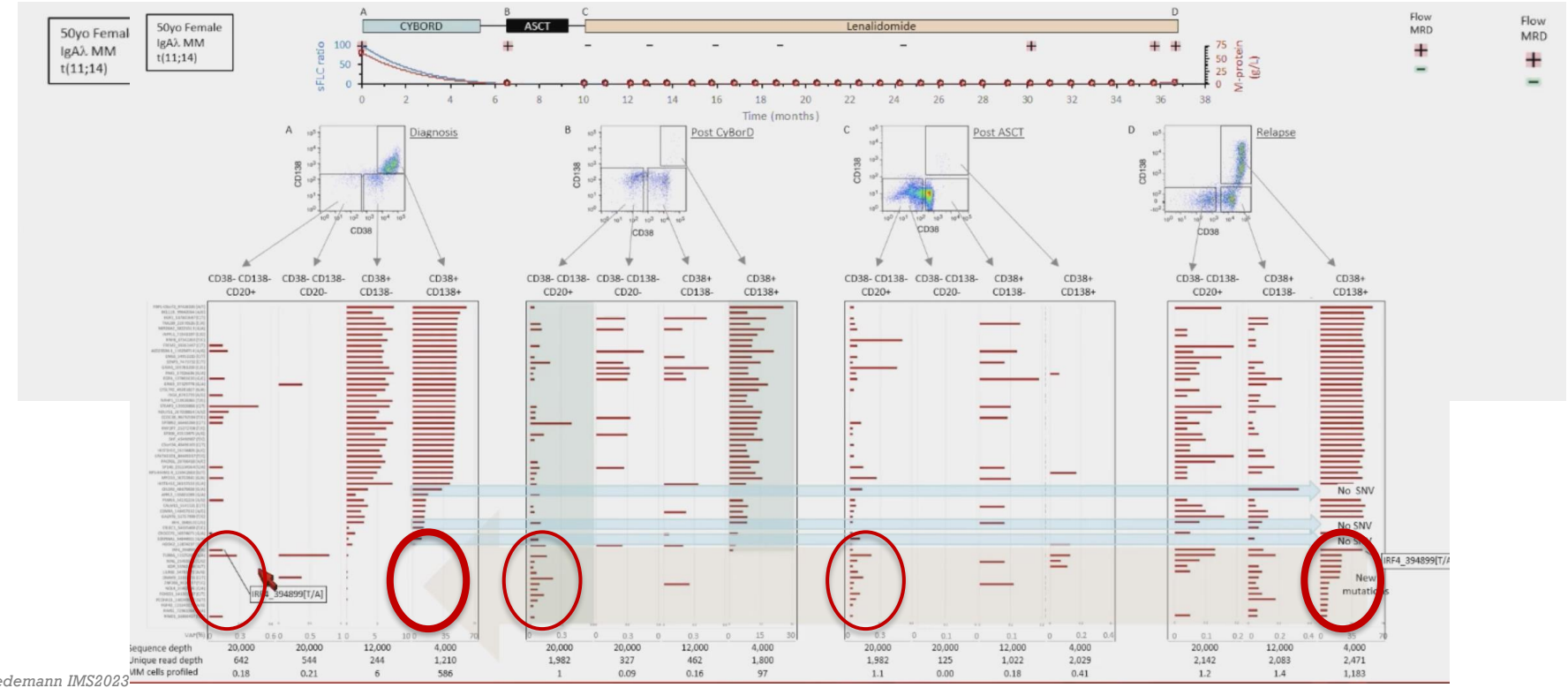

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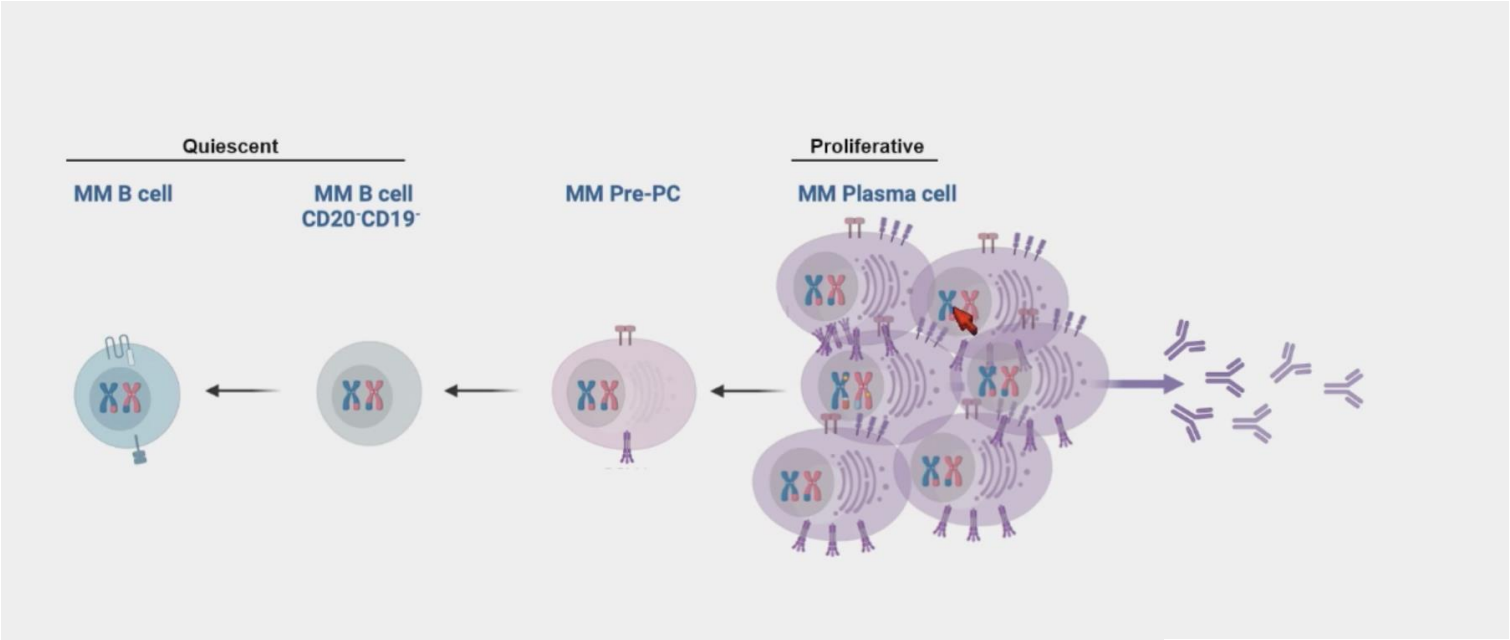
the origin of clonal heterogeneity

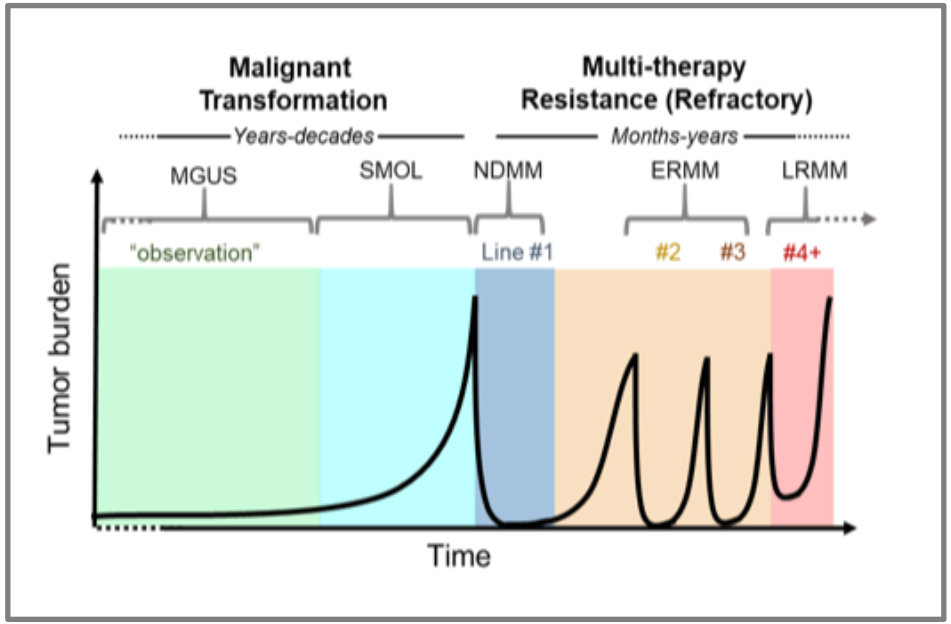
a model of disease progression



R. Tiedemann IMS2023

outline of the presentation

the disease dynamics of MM: clonal evolution



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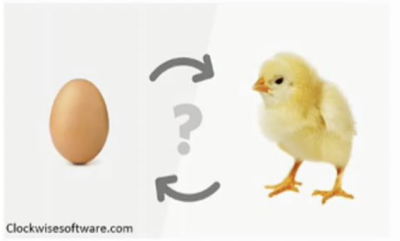
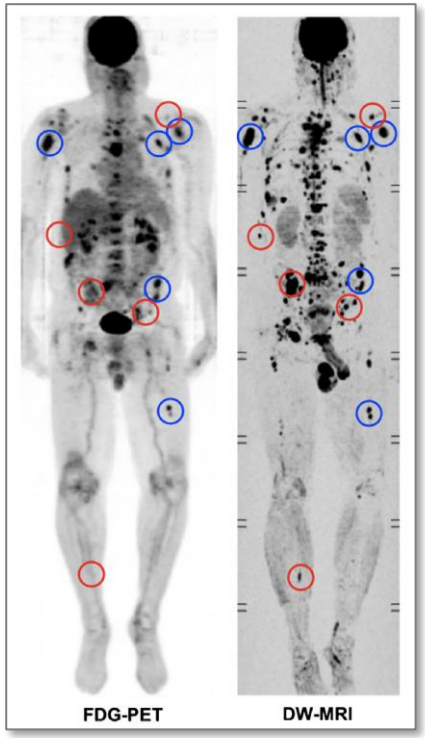


disease dissemination: a role for CMMCs?



spatial heterogeneity in MM

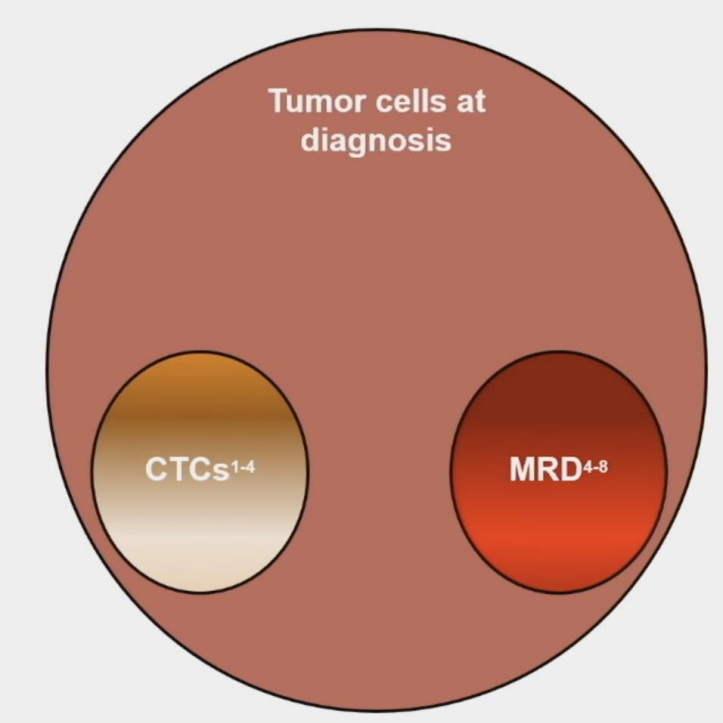
1. number, size, location in the skeleton, type and metabolism of FLs ***differ*** between patients
2. intra-tumoral & spatial heterogeneity can be influenced by local ***TME***
3. specific ***genomic profiles*** are associated to FLs, demonstrating spatial heterogeneity in the TME
4. PCs in different BM sites have different ***transcriptional*** signature & epigenetic ***plasticity***

➔ *the intra-patient disease **dissemination** is a "clonal evolution" process*

C.M.Schurch et al., Virchows Archiv, 2020
L.John et al., Nat Comm, 2023

CMMCs & disease dissemination

MRD & CTCs: *small clones* associated with high risk of relapse



C. Guerrero et al. ASH2023

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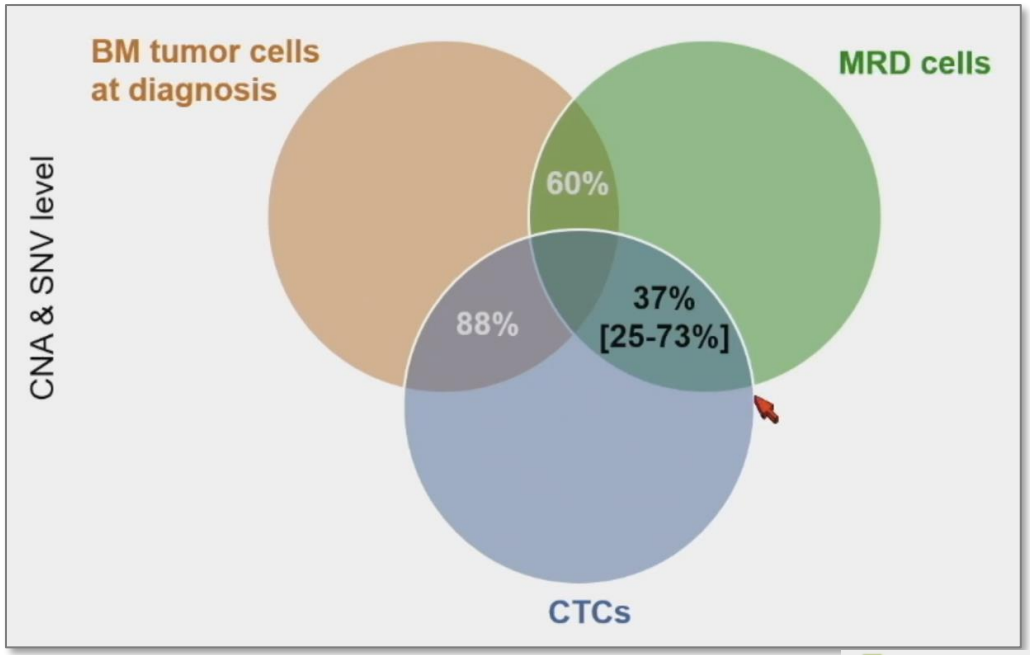
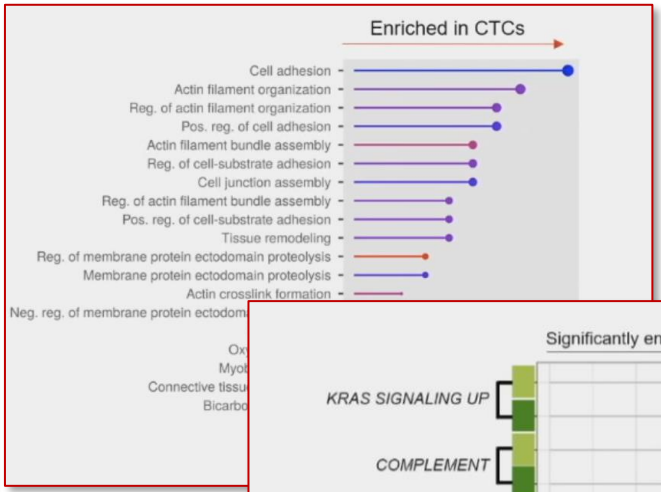
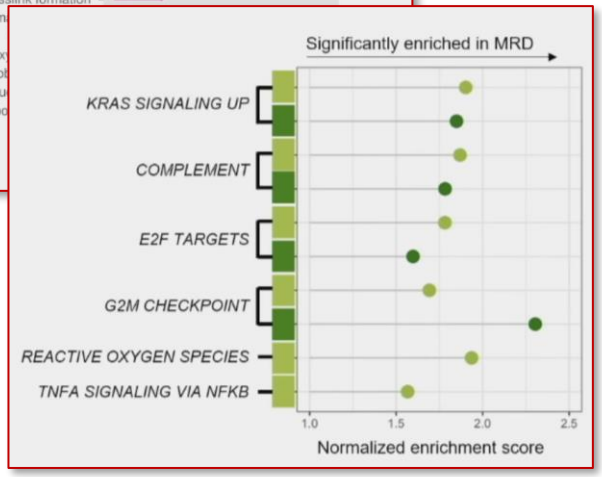




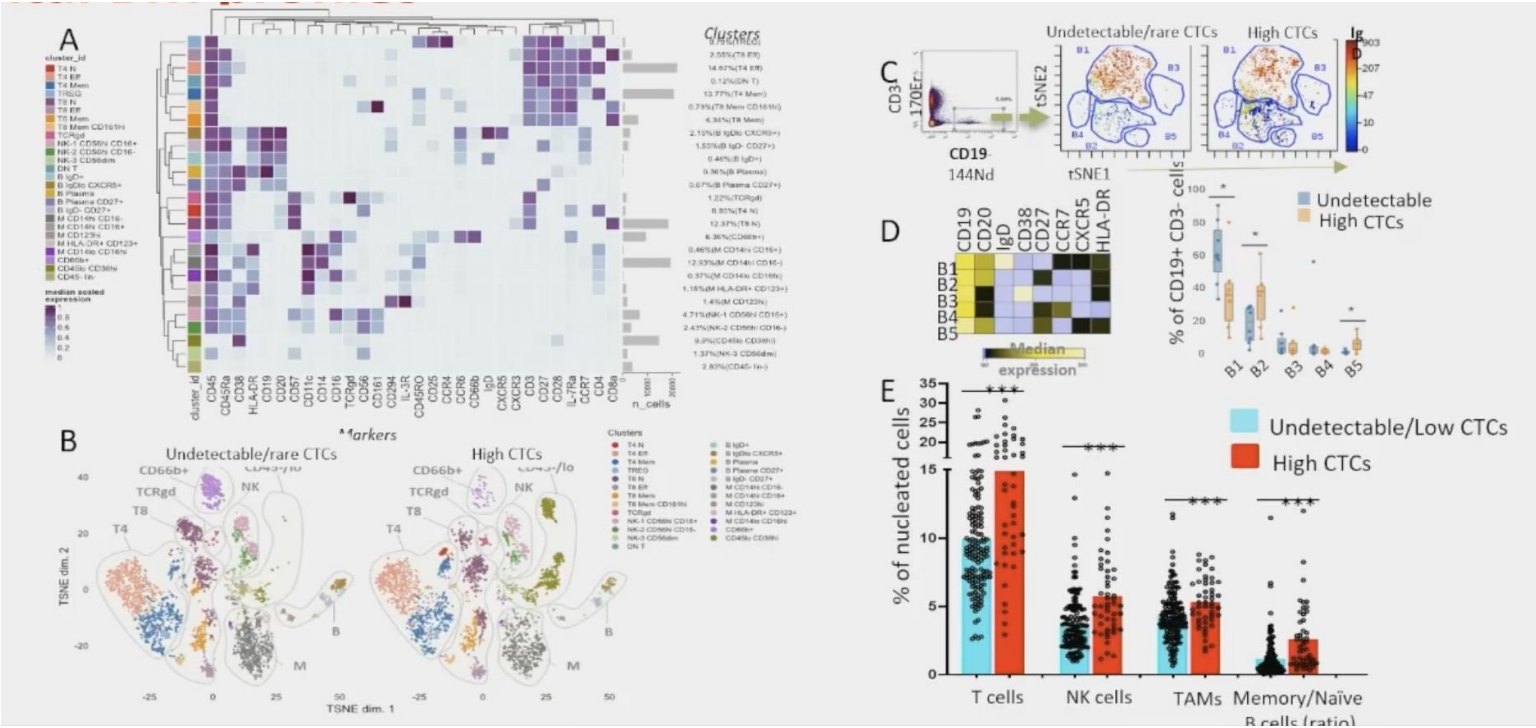


BM tumor cells vs MRD cells post-induction
BM tumor cells vs MRD cells post-HDT/ASCT

C. Guerrero et al. ASH2023

disease dissemination: a role for CMMCs?

CMMCs levels & TME profiles



I.V.Kostopoulos et al., IMS2023
Terpos et al., ASH2023

take-home-message

1. MRD is one of the most important ***bottleneck*** impacting the disease progression

2. resistant clones ***either*** might have emerged under therapy ***or*** might have been already present before therapy

3. in MM are present ***immature*** intra-tumor subpopulation that are ***plastic*** and can differentiate and de-differentiate into other MM subpopulations

4. CMMCs can contribute to the intra-patient disease dissemination